

# HCV/HIV Today

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## The Importance of Water

Kara Wright, PA-C

Water is one of the most important things we take in on a daily basis. We all know we could live a few days without food, but without water, we are sure to suffer quickly. Our bodies are made up of about 70% water. That tells you how important the nutrient rich substance is. Water is especially important for people who have liver disease—whether on or off interferon treatment. It provides many important functions, which we will discuss here.

Water can actually help decrease fluid retention. At first glance, this seems counterintuitive. It doesn't seem like you should drink more water when you are retaining water, but it is true. When the body gets less water, it perceives this as a threat and begins to hold on to all the water it can. When this happens, the body tends to store water outside of our cells, which often causes swollen feet, legs and hands. Drinking more water will decrease the threat and allow the body to release the excess stored water, which decreases the swelling. Increases in salt intake can also cause water retention. In order to alleviate the symptoms, you should drink more water to dilute the effects of the salt. If

this occurs often, you should be cautious with your salt intake. Some people are on restricted water and sodium intakes due to specific disease states. Talk with your provider before changing any dietary recommendations.

One of our liver's primary functions is to rid the body of toxins. Water can help the body get rid of waste products and toxins as well, which helps the liver be more efficient. By staying hydrated, we can help the body efficiently shed all of the extra metabolized products and toxins.

Water suppresses the appetite. Many people feel hungry when, in fact, they are actually thirsty. Drinking a glass of water will often satisfy that sensation and decrease the desire for unnecessary calories. It also helps the body metabolize stored fat. Some studies show that a decrease in water intake will cause fat deposits to increase while an increase in water intake can reduce fat deposits.

Water can help the GI tract function better. When we are dehydrated, the body tries to keep all the water possible. As waste is going

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through the colon to be eliminated, water is absorbed to form solid stool. When we are dehydrated, too much water is absorbed causing very hard, dry stool, or constipation. By giving the body an adequate supply of water, we can prevent this from happening.

Dry skin is a common problem, particularly in patients on interferon treatment. Drinking water can help to moisturize the skin naturally and decrease the side effects, such as itching and flaking.

Water can help regulate body temperatures. During the hot summer months, it is more important to drink water in order to keep the body cool. We tend to dehydrate much more quickly in hot temperatures, and most people don't even realize it. You don't have to be sweating to get dehydrated, so be aware and drink more water. You should increase the amount you drink if you exercise since this is another source of dehydration.

Patients on interferon monotherapy or combination therapy should be very aware of the body's need for water. Simply drinking more water can decrease many of the side effects experienced on treatment. Many patients find it helpful to drink the highest volume of water for 1-2 days after the injection of interferon and then to continue to keep hydrated through the rest of the week.

As you can see, water is very important. How can you determine your body's water needs? There are many different ways to calculate this, but one formula is to divide your weight in pounds by 2 to determine the number of ounces you need to drink in a day. For example, if you weigh 180 pounds you will need to drink 90 ounces of water. That converts to eleven 8 oz glasses a day or  $\frac{3}{4}$  of a gallon a day. (To help you convert ounces to cups or gallons, please go to this website [www.easysurf.cc/conv13htm#fotog1](http://www.easysurf.cc/conv13htm#fotog1).)

Another way to tell if you are adequately hydrated it to check the volume and color of your urine. The urine should be clear or pale yellow in color, and there should be lots of it. The darker and less frequent your urine, the more dehydrated you are.

It is easy to keep track of your water intake. Purchase a sport bottle with the amount of fluid already measured

for you. For example, most store bought water bottles tell you how many ounces of water they contain. Just keep filling up the water bottle and keep track of how many bottles you went through. It is a good idea to keep a bottle at home, one at work, and one in the car.

Don't wait until you feel thirsty to drink water. At that point, you are already slightly dehydrated and you will have to drink extra water just to catch up. The body does not have a strong thirst mechanism to tell you when you are dehydrated, so you must consciously drink water all day to ensure you are hydrated. Drink before you get thirsty. Most people will feel that they are using the restroom very frequently. This is healthy. You should decrease your water intake 1-2 hours prior to bed, so you don't disturb your rest by having to get up to urinate throughout the night. If you know you will be somewhere in which a restroom is not easily accessible, you may wish to stop drinking water about 1 hour before your trip.

It is very important to avoid caffeinated drinks such as coffee, tea and cola. These beverages act as dehydrators by pulling water out of your system. Also, sodas and coffee can cause headaches and diarrhea. If you are sick of drinking water, you can substitute other clear liquids. Be leery of sports drinks as they typically contain lots of sugars and sodium, which can cause dehydration as well. Drink these in small amounts.

If you have congestive heart failure, kidney disease, decompensated liver disease or ascites (fluid accumulation in the abdomen), it is very important that you speak to your medical provider before increasing your water intake. Patients with these illnesses are often on restricted water protocols due to the disease state.

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# Questions to Ask your Healthcare Professional

Kara Wright, PA-C

The diagnosis of hepatitis C can be overwhelming. Many people are shocked at the time of diagnosis and have difficulty understanding all of the implications at first. After adequate time to process the information, patients should do a little research to learn more about the disease. After this research, it is important to sit down with your healthcare provider to learn more about this diagnosis. To help you get started, here are some important questions you may want to ask.

## General Hepatitis C Questions

- ◆ How does my diet affect the hepatitis C virus?
- ◆ May I be referred to a dietitian or nutritionist for help with my dietary needs?
- ◆ How do my social habits (drinking alcohol, using drugs, and smoking) affect my liver or the hepatitis C virus?
- ◆ Do I need to stop drinking alcohol completely? If I want to stop using alcohol and/or other drugs, can you refer me to an alcohol and drug counselor?
- ◆ If I want to stop smoking, can you refer me to someone to help me quit?
- ◆ Do I have to change my sexual practices?
- ◆ Should my partner(s) be tested?
- ◆ What kinds of symptoms/signs can I expect now that I have been diagnosed with hepatitis C?
- ◆ What if I feel fine? Does that mean my liver is not damaged?
- ◆ Is there a support group in the area that I can attend?

## Other Infections

- ◆ Do I need to be tested to see if I am immune to hepatitis A and/or hepatitis B?
- ◆ Am I immune to hepatitis A and/or hepatitis B? If not, do you recommend I be vaccinated for either or both the hepatitis A and B viruses?
- ◆ Should I be tested for HIV or other infections?

## Questions about Labs

- ◆ What is my hepatitis C viral load?
- ◆ How often should I have my viral load checked?
- ◆ What is my hepatitis C genotype? (This is a one-time liver test.)
- ◆ How does my genotype affect my illness and pos-

sible treatment?

- ◆ What are my liver function test levels? (Liver function tests are ALT/AST, ALP, and SGTP, bilirubin, albumin, and prothrombin time.)
- ◆ How often should I have liver function tests done?

## Questions about a Liver Biopsy

- ◆ Do you recommend I have a liver biopsy?
- ◆ If yes, why?
- ◆ If no, why not?
- ◆ What is involved in getting a biopsy?
- ◆ What are the risks?
- ◆ How is the procedure performed?
- ◆ How long does the procedure take?
- ◆ What experience do you have, or does the doctor performing the procedure have in doing liver biopsies? (The more experience they have, the better.)
- ◆ If a liver biopsy shows that I have fibrosis or cirrhosis (scarring), how does that affect my treatment options?
- ◆ (If you have already gotten a biopsy) What are the results of my liver biopsy and what does it mean? Will the result affect my treatment?
- ◆ May I have a copy of the biopsy report for my records?

## Questions about Treatment

- ◆ Do you feel I am a good candidate for interferon and ribavirin combination therapy? What about pegylated (peg-a-lated) interferon therapy?
- ◆ If so, why?
- ◆ If not, why?
- ◆ What are the pros and cons of beginning treatment?
- ◆ What are the potential side effects of interferon and ribavirin, or of pegylated interferon?
- ◆ How long do you think I will have to be on therapy?
- ◆ How is the treatment taken?
- ◆ How may the treatment affect my life and my lifestyle?
- ◆ What is the likelihood that the treatment will be successful?
- ◆ Should my partner or I practice birth control while

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## HealthWise: Food for Thought

Lucinda K. Porter, RN, CCRC

Exercise! The very thought of it can induce tears in those who do not enjoy physical activity. For those who have medical issues, exercise is an even more complicated venture. People living with hepatitis C report fatigue, muscle and joint aches. Depression, weight gain, and mental "fogginess" can also create obstacles. We know that physical fitness is "good for us." Healthcare professionals recommend exercise. Insurance companies and employers promote physical fitness because ultimately it is good for business. Just pick up a newspaper or turn on the TV and it's clear that athletes and sports are a popular part of our culture. Even the office of the President encourages exercise and has done so since 1956 with the creation of what is now known as the President's Council on Physical Fitness and Sports. Regular exercise is known to have a positive influence on a number of medical problems including arthritis, osteoporosis, back pain, diabetes, depression and cardiovascular disease. Certain fitness programs can improve flexibility, balance, tone, strength and stamina. Being physically active may improve sleep, reduce food cravings, and help us feel more energetic.

If this is true, then how do we get moving? The key may be the way we perceive exercise. If we view exercise as a chore or something that creates pain, then physical activity may feel like an obstacle. Perhaps the first step is as simple as replacing the words "exercise" and "fitness" with "play" and "fun." If exercise is seen as an act of recreation or play, it might help us to move in the right direction.

Being willing to move is important but not enough to propel us off the couch. How do we get started? First and foremost, consult your health care practitioner. There may be medical reasons to limit or modify a fitness program. After medical advice is given then develop an action plan.

Start by setting short- and long-term goals. Goals should be reasonable, specific, measurable, and time-limited. Start small and gradually work up to a goal. If the long-term goal is to walk 30 minutes four days a week by the end of the year, then 5 minute walks 3 days a week for the next month is an example of a short-term goal. Attaching a reward to accomplishing the goal can be motivating. The reward can be something small, but still desirable. Choose a healthy reward. A hot bath may be a better choice than a piece of chocolate cake. Other examples are new exercise clothes, like socks or a warm-up jacket; exercise gadgets, such as a pedometer or a heart rate monitor; and

additional time for relaxation or engaging in a favorite activity.

Evaluate the goal. If the goal is reached, collect the reward as well as congratulations. What made the goal attainable? If the goal is not met, evaluate the reasons. Was the goal realistic? Is it a goal worthy of commitment? What interfered with reaching the goal? Can something be done differently that will make the goal more achievable? Perhaps the goal was too big and needed to be broken down into smaller parts. Whether the goal is met or not, praise is important. The effort alone has merit. After goal assessment, set another or commit to the same goal. Continue to celebrate every victory.

Here are some other suggestions, especially when it is hard to maintain a fitness program:

- ◆ Show up and suit up. Some people find the act of putting on sneakers and starting the activity helps overcome mental resistance.
- ◆ Find a fitness buddy. We are less likely to cancel out on a friend than we are on ourselves.
- ◆ Join a group or class.

Common types of exercise focus on strength, flexibility, balance and aerobic endurance. Some activities combine all of these elements, while others concentrate on one aspect. It is advisable to begin exercise by warming up and to practice the habit of stretching and cooling down. For those new to exercise, a reasonable beginning regimen might be to walk a few minutes, stretch, and call it a day. Always allow a day of rest between weight training workouts. Some fitness trainers recommend a day of active rest every week. Active rest means taking a break from a regular fitness regimen but does not mean spending it all on the couch.

Walking, hiking, swimming, dancing, bicycling and weightlifting are some common recreational activities. Physical fitness is more likely to be successful if it is portable, not dependent on the weather, and fits any budget. Staying fit does not have to be an all or nothing proposition and can fit into the busiest schedules. Some ways to do this include gardening, using the stairs, choosing a parking spot on the outskirts of the lot, getting off the bus before the scheduled stop and walking the rest of the way, window shopping, sweeping the floor, and mowing the lawn. Replace power tools with manual tools. Mowing the lawn with a push

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mower is an excellent way to be active. Walk instead of driving. Don't use the remote control when watching T.V. Talking on the phone or watching television are excellent opportunities to stretch, do leg exercises or lift light weights. Any opportunity to be active helps us to stay in shape.

Just as in life, variety is an important aspect of exercise. If you walk, add activities at various intervals that increase your heart rate and use other muscles. Examples of this: Every 5 minutes of walking, try skipping for a minute, or do 4 lunges, or 2 minutes of speed walking. If you use weights for toning, try a session using light weights with 20 to 30 repetitions, and another session using heavy weights and perhaps only 5 or 6 repetitions. You can also vary the speed of your workout. Lifting weights at a very slow rate can be incredibly challenging. Some local parks and trails have workout stations call "par courses." These are free and a simple way to add variety to your walk or run.

Be sensible about exercise. Remember to drink water, apply sunscreen and avoid injuries. Pain is NOT gain. However, sore muscles may occur. Heat, cold packs, and stretching may be beneficial. Remember to consult a doctor for injuries and discuss a back-up fitness plan

for common injuries. Avoid exercise when ill.

Videos, magazines and books can be useful resources. Choose sources that target your age and fitness needs. I read *Prevention* magazine because it is practical, motivating and easy to carry around with me. Many communities and employers offer groups and classes. The Internet has informative sites. Try doing a general search using "exercise" or "physical fitness" as key words. Information about *The President's Council on Physical Fitness and Sports* and the *President's Fitness Challenge* can be found at the end of this article. Information for people with disabilities is provided on The President's Challenge web site.

We have access to a coach 24 hours a day. It is the one we carry with us. Most of us respond to a supportive coach. Skip the criticism. Show up, suit up and keep a positive attitude. The effort is worth it, especially when fitness becomes fun. [www.fitness.gov](http://www.fitness.gov). and [www.presidentschallenge.org](http://www.presidentschallenge.org)

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on the medications?

- ◆ Can my partner (or I) get pregnant safely while I am on the medications?
- ◆ Do you exclude patients from interferon/ribavirin or pegylated interferon treatment if they have advanced liver scarring?
- ◆ If I have a history of mental health issues (depression/anxiety), will I be a candidate for hepatitis C treatment?
- ◆ How will my mental health be managed?
- ◆ What will be done if my mental health gets worse?
- ◆ If I am on methadone, how will this affect my eligibility for hepatitis C treatment?
- ◆ How do you feel about treatment for hepatitis C while a person is on methadone?
- ◆ Will you work together with my dispensing/treatment agency to coordinate my care?
- ◆ Are there new therapies that will soon be available, and do you think I should wait for them?
- ◆ While on treatment, how often will I need to return for follow-up?
- ◆ What should I do if my health gets worse between now and the next time I see you?
- ◆ Are you available by phone?
- ◆ What should I do if I have side effects? Is there anything I can take to help the side effects go away?
- ◆ Is there anything I can do on my own to help—such

as changes to my diet, etc?

### **Questions about Emotional Issues**

- ◆ Where can I find emotional support for my family and for me?
- ◆ How can I expect this to affect my marriage or other intimate relationships?
- ◆ How do I explain my diagnosis to friends and family?
- ◆ Are there any clinical trials I could participate in?
- ◆ Who from your office can I speak with if I have questions or concerns about my treatment?

### **Questions about a HealthCare Provider's Experience with Hepatitis C**

- ◆ Do you have many other patients with hepatitis C?
- ◆ Do you feel up-to-date on all the latest changes and advancements in hepatitis C treatment?

Now that you are armed with some questions to ask, you may wonder how to ask these questions. Providers can sometime appear intimidating and may make you feel they are rushed. Be confident. Providers are usually more than happy to take the time to answer any questions or schedule time to answer questions later, perhaps by email or phone.

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## Research Findings Suggest New Hepatitis C Drug's Potent Antiviral Activity

The investigational hepatitis C viral (HCV) protease inhibitor VX-950 exhibits potent and sustained antiviral activity in vitro and has favorable pharmacokinetic properties, according to preclinical results presented by scientists from Vertex Pharmaceuticals (VRTX) at the Annual Meeting of the American Association for the Study of Liver Disease (AASLD) in Boston, MA.

In addition, researchers reported that VX-950 retains full in vitro potency against HCV replicon strains resistant to another investigational HCV protease inhibitor currently being developed by another company. Vertex plans to initiate clinical studies of VX-950 in early 2004.

"As we prepare to advance VX-950 into initial clinical evaluation, these preclinical results provide information that is in line with the treatment goal for this disease: clearing the hepatitis C virus from the liver," said John Alam, MD, senior vice president, drug evaluation and approval of Vertex.

"Although significant progress has been made in recent years with combination therapy regimens, nearly half of HCV patients currently treated with the standard of care, pegylated interferon plus ribavirin, fail to achieve a sustained response. Direct antivirals represent the potential for a dramatic breakthrough in the treatment of HCV.

"HCV protease inhibitors, such as VX-950, could usher in a significant treatment advance for patients with HCV."

In a conference presentation entitled "VX-950: A Tight-Binding HCV Protease Inhibitor with a Superior Sustained Inhibitory Response in HCV Replicon Cells," virologist Ann Kwong, PhD, head of cell biology and infectious disease at Vertex, reported the first data using an innovative adaptation of the HCV replicon assay commonly utilized to measure the potency of antiviral compounds against HCV.

Vertex scientists used the HCV replicon assay system to evaluate how HCV protease inhibitors sustain potency over a period of 4 weeks. In these experiments, HCV replicon cells, which mimic the intracellular replication of HCV, were treated with VX-950 and were evaluated at multiple time points.

In one experiment, treatment with VX-950 for nine days reduced HCV RNA by almost 10,000-fold (4

log<sub>10</sub>). In another experiment, HCV replicon cells treated with VX-950 for 13 days exhibited viral clearance at day 13, and no rebound of HCV viral RNA was observed at day 27.

Dr. Kwong also described the development of a novel preclinical HCV protease expression model that was designed to stringently evaluate the ability of small molecule compounds to inhibit HCV protease in liver tissue. VX-950 dosed orally resulted in a significant, dose-dependent inhibition of an HCV-protease enzyme-dependent signal.

In untreated control models, high concentrations of active HCV protease enzyme over seven days were associated with significant liver damage. However, treatment with VX-950 for the initial three days of the experiment resulted in sharply reduced liver damage. These data are the first to suggest that an HCV protease inhibitor may have a tissue-sparing effect on the liver. The mechanism by which this occurs is currently under investigation.

Additional data presented at the meeting by Vertex researchers demonstrated that the viral resistance profile of VX-950 is different from the resistance profile of the HCV protease inhibitor BILN-2061 in HCV replicon cells. VX-950 was able to inhibit HCV replicons containing the dominant mutation observed for BILN-2061 to the same degree as inhibition of wild type replicons. BILN-2061 is an investigational HCV protease inhibitor being developed by another company.

VX-950 is an oral, small molecule protease inhibitor discovered by Vertex using structure-based drug design. Vertex was the first to solve the structure of the hepatitis C NS3-4A protease domain, an enzyme that is essential for HCV viral replication.

In addition to potent activity observed in vitro, preclinical testing conducted to date shows that VX-950 achieves excellent exposure in the liver, the target organ for HCV treatment, good oral bioavailability and favorable pharmacokinetic properties.

Vertex Pharmaceuticals Incorporated is a global biotechnology company committed to the discovery and development of breakthrough small molecule drugs for serious diseases.

*This article was prepared by Drug Week editors from staff and other reports, November 28, 2003*

## Data Reported from Phase IB Trial of Isatoribine

Anadys Pharmaceuticals, Inc., at the HEP DART 2003 Meeting on Frontiers in Drug Development for Viral Hepatitis in Kauai, Hawaii, reported interim results from an ongoing clinical trial of isatoribine (ANA245) that demonstrated that the drug is well tolerated and safe at all doses that were studied.

Although efficacy is not a stated objective of the phase IB clinical trial and the number of patients were small, results also showed that isatoribine reduced viral load in patients with chronic hepatitis C virus (HCV) infection. Isatoribine is believed to act by a mechanism involving interaction with Toll-like receptor 7 (TLR7) to stimulate the patient's own immune system, and is one of a new class of drugs being developed by Anadys to regulate innate immunity, combat HCV infections and overcome limitations of current therapies.

Although the results of preliminary clinical trials are not necessarily predictive of results from later-stage clinical trials with larger patient populations, Anadys is encouraged by these early results, and believe they provide proof of concept that a compound interacting with TLR7 can reduce viral load in HCV infected patients. The results were presented at the meeting by Bradley M. Kerr, PhD, Anadys' senior director of clinical affairs.

In an oral presentation, Kerr presented interim data from a cohort treated with 800mg of isatoribine once daily, the highest dose planned in an ongoing dose escalating open-label phase IB clinical trial of isatoribine administered intravenously over a period of 7 days to adults with chronic HCV infection.

The phase IB clinical trial is being conducted at two clinical centers in Western Europe, and to date viral load data is available from a total of 19 HCV infected patients who have been dosed in four cohorts at 200 mg, 400 mg, 600 mg, and 800 mg doses. The results reported by Anadys corroborate and extend previously disclosed safety, tolerability, and pharmacokinetic data derived both from single doses of isatoribine in healthy volunteers, and at lower doses in the current multiple dose phase IB trial in HCV infected persons.

Isatoribine treatment was well tolerated, with no serious adverse events and a low frequency of mild to moderate adverse events. Although efficacy is not a stated objective of the phase IB clinical trial, at the 800mg dose isatoribine showed a statistically significant decrease in viral load in 6 HCV infected patients.

Plasma viral load declined during treatment in all patients who received the 800mg dose of isatoribine. The viral load difference between the beginning and the end

of treatment was statistically significant ( $p=0.03$ ), with a median change in viral load from baseline of  $-0.94$  log<sub>10</sub> units. The reduction in viral load confirmed the favorable trend seen at lower doses, and was accompanied by changes in biologic markers of antiviral immune response, similar to results seen at lower doses.

"The viral load reduction data generated in this trial provides strong support for the continued development of isatoribine, particularly since it represents a new class of agents for the treatment of infections by hepatitis C virus" said Yves Horsmans, MD, professor, Cliniques Universitaires St. Luc, Belgium, and Principal Investigator of the study.

Isatoribine is a patented nucleoside analog Anadys is developing for the treatment of HCV infection. Isatoribine is one of a new class of drugs being developed by Anadys to regulate innate immunity, combat HCV infection and overcome limitations of current therapies. Anadys believes isatoribine interacts with a specific receptor, Toll-like receptor 7, or TLR7, that is present on certain immune system cells.

Although results of initial clinical trials are not necessarily predictive of future results, interim results of this ongoing phase IB clinical trial showed that isatoribine reduced viral load in HCV infected patients. Anadys is encouraged by these early results, and believe they provide proof of concept that a compound interacting with TLR7 can reduce viral load in HCV infected patients. Anadys expects to initiate a phase I/II clinical trial of isatoribine in selected populations of HCV patients in the beginning of 2004.

HCV causes inflammation of the liver and degradation of liver function. HCV infection is currently the most prevalent chronic blood-borne infection in the U.S. Approximately 2.7 million people in the U.S. are chronically infected with the HCV, and it causes 10,000 to 12,000 deaths a year in the U.S.

The Centers for Disease Control (CDC), studies estimate the annual mortality rate could increase to 38,000 by the year 2010, surpassing the number of deaths attributed annually to HIV/AIDS. The HCV is transmitted primarily through significant or repeated exposures to infected blood. Approximately 2/3 of new infections progress to chronic infection. Chronic HCV may also progress to more serious complications such as cirrhosis of the liver, liver cancer, and death.

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## HealthWise: Hepatitis C and Aging

Lucinda K. Porter, RN, CCRC

"To me, old age is always 15 years older than I am." - Bernard M. Baruch

According to the most recent census, there are more than 35 million adults age 65 and over in the United States. By the next census in 2011, Baby Boomers will push this growth to notable numbers as this group reaches the age of 65. The National Institutes of Health (NIH) Consensus Conference on the Management of Hepatitis C (HCV) reported that the highest prevalence of HCV occurred in persons age 40 to 59. This means that by the 2011 census, the U.S. population will have record numbers of aging adults living with HCV. This group includes a high prevalence of African Americans and Veterans, groups that already have unique health problems without the extra burden of an HCV diagnosis.

The aging process has an impact on every body system. Older adults experience eye, skin, and gastrointestinal problems. Immune and cardiovascular systems become affected. Bladder, bowel, and brain functions can become impaired. Arthritis, insomnia, depression and sexual dysfunction are reported more frequently in older adults. Our bodies are somewhat like automobiles. The better you take care of your car, the longer it is more likely to last. However, sooner or later various parts start to break down. In *Reader's Digest*, Gloria Pitzer sums up the process well when she said, "About the only thing that comes to us without effort is old age."

People living with HCV may report various symptoms that accompany this viral infection. There are some similarities between the medical problems incurred by aging and those of chronic HCV infection. An area worth exploring is the relationship between aging and HCV.

At the American Association for the Study of Liver Diseases (AASLD) 2003 conference, Dominique Thabut and colleagues from Groupe Hospitalier Pitie-Salpetriere, Paris, France reported that in patients 65 years or older, chronic hepatitis C is more severe and presents with lower ALT levels than in younger patients. This report was based on data collected from 2,410 people living in France. The report also stated in the conclusion that treatment is effective and well-tolerated. Additionally, the use of biochemical markers may be useful as a non-invasive alternative to liver biopsy in this population.

The age at which HCV was acquired may have an impact on prognosis. A number of studies have reported that individuals who become infected with HCV at older ages tend to have a worse prognosis than those who acquire HCV while young. The NIH HCV Consensus report lists people over age 40 among those who are more likely to develop HCV-related liver cancer. Age can also have a negative impact on liver transplantation survival. In a study from Spain, Ignacio Herreroa and colleagues reported in the November issue of the *American Journal of Transplantation* that older liver transplant recipients have a significantly lower survival rate than younger patients.

Treatment for older adults living with HCV has dimensions that occur less frequently in younger adults. Some physicians are reluctant to treat elderly HCV patients. The current standard treatment of pegylated alpha interferon and ribavirin carries some risks. Couple the list of treatment side effects with the list of changes that occur during aging and the overall picture becomes more complicated. The NIH HCV Consensus report states that patients over the age of 60 years old should be managed on an individual basis.

Another consideration of HCV treatment for older adults is life expectancy. Just like certain models of cars, some individuals can expect to live longer. Further, a report in the medical press preliminarily suggests that life expectancy may be increased in chronic hepatitis C patients undergoing interferon therapy by preventing liver-related deaths.

Regardless of age, treatment decisions are always between the medical team and the patient. These decisions are individualized, based on multiple factors. The impact of age is a component of the decision-making process. Hopefully as new treatments develop, there will be more and easier to tolerate options available to aging persons living with HCV. Until that time, take good care of yourself. We all know that life is short. In the words of Maurice Chevalier, "Old age is not so bad when you consider the alternatives."

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## HIV Bites

### A Protein Resistant to AIDS

Editor Note to the Reader

One of our technical reviewers drew attention to a short, but interesting, article on HIV that appeared in The Washington Times newspaper dated February 26, 2004, titled "Protein resistant to AIDS discovered." The article refers to a Harvard study published "today" in the journal "Nature." The article is worth reading and can be accessed via the internet at [www.washingtontimes.com](http://www.washingtontimes.com)

The study appears in Nature, Vol. 427, 26 February 2004, pages 848-853. The abstract states, in part: "Human immunodeficiency virus type 1 (HIV-1), the cause of acquired immunodeficiency syndrome (AIDS) in humans, efficiently enters the cells of Old World monkeys but encounters a block before reverse transcription." The wording of the study is very technical.

An article referring to the study appears on pages 791 and 793 in the same issue of Nature and is helpful in understanding the importance of the study. This article is titled "Replication trimmed back," by Stephen P. Goff from the Columbia University College of Physicians and Surgeons in New York. A gene known as "TRIM5alpha" was isolated by the study referenced above and "may lead to new approaches towards inhibiting HIV-1." This article goes on to state that not much is known about TRIM proteins, but "A look through the human genome reveals at least 37 TRIM family members." The article goes on to postulate about the possible mechanisms accounting for the effectiveness of TRIM5alpha in the rhesus macaque monkeys used in the study and ask some of the questions needing answers. The article ends by saying, "All we can say for certain is that right now many laboratories are working furiously to be the first to find answers to these questions. When the mechanism of action of TRIM5alpha is uncovered, the next goal will be to recreate its effects in a therapeutic treatment."

### Once-A-Day Therapy: Now or Later?

(From *Numedx, Spring-Summer '03*)

In order to have virologic suppression of HIV, adherence of 95 percent or higher to HIV therapy is required. We have learned from other chronic conditions that when the pill regimen is simple, adherence is improved. We can generalize from the hypertension studies that as regimens for HIV become sim-

pler, medication adherence will improve.

There are now 21 drugs available to slow down the replication of HIV in humans. Seven of these drugs, in three drug classes, are FDA approved for one daily use. They are the nucleosides (NRTIs) lamivudine (Epivir), stavudine XR (Zerit XR), didanosine ED (Videx EC), and emtricitabine (Emtriva); the nucleotide tenofovir (Viread); the non-nucleoside (NNRTI) efavirenz (Sustiva), and the protease inhibitor boosted amprenavir (Agenerase).

The move to once-daily dosing is gaining popularity among treatment-experienced and treatment-naïve patients. A drug should be powerful enough to work (i.e., it should have a long enough half-life) even if a person misses a dose. Half-life is the amount of time it takes for half a dose of a drug to be eliminated from the body.

Preliminary reports suggest the following combinations can be taken once daily and are effective in reducing the viral load and in maintaining CD4 cell count: (This list was compiled before the approval of Emtriva in July.)

- Videx EC + Viread + Sustiva
- Videx EC + Epivir + Sustiva once daily
- Viread + Epivir + Sustiva
- Videx EC + Viread + Agenerase
- Viread + Epivir + Invirase + Norvir
- Videx EC + Epivir + Agenerase + Norvir
- Videx EC + Epivir + Viramune once daily.

A new protease inhibitor, Atazanavir, is in Phase III clinical trials. Other drugs are being studied for once-daily use, but their once daily efficacy has not been proven and such use is considered "off-label." These drugs include zidovudine (Retrovir), abacavir (Ziagen), and lopinavir/ritonavir (Kaletra).

Patients should consult with their healthcare provider and not make treatment decisions based solely on how easy the regimen will be. All factors should be taken into consideration: what kind of schedule the person has, what other medications they may be taking, their ability to swallow pills (many of the medications come in a liquid form and that is also an option for those who have trouble swallowing pills), how high their viral load is, and how low their CD4 cell count is.

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From studies with other medications, we know that be reducing pill burden and by simplifying regimens and dosing frequency, patients can have a good response to their medications.

## Liver Injury Linked to Protease

**Inhibitor Therapy** (From: *NHF notes*, 8/03; Source: *AIDS Weekly*, 8/11/03)

In a recent study published by scientist Mark S. Sulkowski in *Seminars in Liver Disease*, hepatotoxicity (liver injury) has been linked to antiretroviral therapy with HIV-1 protease inhibitors.

"Human immunodeficiency virus 1 (HIV-1) protease inhibitors are important components of highly active antiretroviral therapy (HAART). However, in the era of HAART, drug-induced hepatotoxicity has emerged as an important potential complication of combination antiretroviral therapy, particularly those regimens containing protease inhibitors (PIs)," Sulkowski said.

The study goes on to say that "liver injury has been associated each of the six PIs currently approved by the U.S. Food and Drug Administration (FDA), most commonly with administration of full dose ritonavir (600 mg bid [twice a day] or 400 mg bid with saquinavir). However, this regimen has been largely replaced by the use of low-dose ritonavir (<200 mg bid) to pharmacologically "boost" other PI's, such as lopinavir or indinavir, which have not been associated with an increased risk of hepatotoxicity compared with other PIs. Co-infection with HCV and HBV remains an important risk factor for the development of HAART-associated liver injury."

"Although studies indicate that co-infected patients can be safely treated with PIs, such patients should be closely monitored," concluded Sulkowski. "In addition, although unsubstantiated, some experts recommend evaluation or treatment, or both, of underlying chronic viral hepatitis prior to the initiation of antiretroviral therapy."

## Transplants Give Life to HIV-Infected

Not long ago, the thought of transplanting organs into HIV-patients would have defied all reason. Giving scarce organs to patients who did not have long to live was considered wasteful, even unethical. Yet like so many things about AIDS, that view is slowly giving way to another: "Now, the question is whether we can ethically exclude these patients," said Dr.

Stephen T. Bartlett, a surgeon at the University of Maryland Medical Center who performed a kidney transplant on an HIV-positive patient last May.

The unofficial moratorium on transplants for HIV-infected patients, in force since the 1980s, is slowly being lifted as hospital after hospital has found ways to push boundaries once though inviolable. The argument for performing organ transplants on such patients was strengthened by a study presented this year by researchers at the University of California-San Francisco. Among 23 patients who had at least a year of follow-up after their transplants, the survival rate was about 85 percent. Outcomes overall were no different than one would expect among people without the virus.

The University of Maryland Medical Center has recruited patients for a nationwide trial in which 75 HIV-infected patients would receive kidney or liver transplants. One purpose of the clinical trial is to determine which anti-rejection drugs and which antivirals should be used and in what doses. Many doctors believe that certain anti-rejection drugs do nothing to worsen HIV infection while others should be avoided.

Dr. John Conte, who heads the heart transplant program at Johns Hopkins University, said heart transplants for people with HIV remain risky and should be done only by institutions participating in a clinical trial. For now, he said, the Hopkins program is staying out of trials, preferring to reserve the procedure for patients who stand the best chance of succeeding. (Baltimore Sun, 6.23.03) *Body Positive* Vol. XVI, No. 5, 2003

## HIV and 'Natural' Therapies: A Bad Blend

Half of US patients infected with HIV use alternative therapies while taking powerful AIDS cocktails, and nearly one in four choose alternative treatments that could interfere with conventional AIDS therapy. And many never share that information with their doctors, researchers have found in a recent study.

Patients often believe that so-called natural treatments are helping to keep them healthy and diminishing the unpleasant side effects of prescription drugs. But megadoses of vitamins, homeopathic remedies and some herbs can reduce the effectiveness of antiretroviral drugs. For example, the herbal antidepressant St. John's wort lowers blood levels of protease inhibitors, including indinavir (Crixivan) and ritonavir (Norvir). As a result, the medication can stop working and HIV can

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## Gene Genie

### Can Gene Therapy Deliver a Better Fusion Blocker?

By Bob Huff

If the daily grind of subcutaneous injection of T-20 (Fuzeon) has got you down, why not let your T-cells make their own—with gene therapy? Dorothee von Laer and Marc Egelhofer from Georg-Speyer-Haus in Germany and colleagues recently reported on progress in constructing a vehicle for an artificial gene called C36 that produces a peptide with the same fusion-blocking sequence of T-20 (Fuzeon). The idea is to inject the gene, deliver it to blood cells, and let the cells manufacture a new protective weapon against HIV to place on their outer envelopes.

So far, the field of gene therapy has been beset by false starts and a few tragic incidents, which have left scientists understandably wary about inserting foreign genetic material into people. After all, HIV itself is nothing more than a collection of alien genes that hijack normal cellular activity in order to propagate and multiply; immunological havoc is the result. But von Laer's group has engineered an elegant bit of genetic trickery that not only blocks HIV before it can get its foot in the door, but is carefully designed to minimize unwanted side effects.

Other projects are investigating gene therapies to treat HIV by blocking the expression of viral proteins such as tat. But these approaches would only be able to minimize viral activity after a cell had already become infected. Mathematical models suggest that such downstream gene therapy strategies would cause the proportion of HIV infected cells in the body to steadily increase. Lead author Egelhofer cautions that, as the number of cells harboring integrated HIV provirus grows, the burden of controlling viral expression would become overwhelming. But a fusion-blocking gene therapy that worked upstream of infection would preserve uninfected cells, thus increasing their proportion.

The idea is to attach the 36 amino acid peptide to a hinged transmembrane protein that would allow it to reside on the surface of a target cell. If an HIV virion attaches to the cell and begins the process of bringing its lipid envelope into contact with the cell's membrane, the C36 peptide would jam the gp41 mechanism that mediates fusion—exactly as T-20 does. The advantage is that, rather than injecting the peptide into the body in sufficient concentrations to achieve a high rate of blocked infections, the peptides will be assembled inside target cells then exported to the cells' surface, precisely where they are needed.

The genes that code for the production of C36, the hinge and other supporting members, are cleverly delivered to the cell by a retroviral vector that gains entry by attaching to cells bearing the CD34 cell surface protein. Once inside, the vector deposits its genetic cargo, which is then shipped to a protein processing factory in the cytoplasm. The finished gene product is delivered back to the cell surface and implanted in the membrane, where it is free to move about and interact with any encroaching gp41s.

After an initial demonstration of the concept with a construct that inhibited infection in a limited set of cell types, van Laer and colleagues have now created an optimized version of the therapy that works in a broader range of primary cells and HIV isolates. The design improvements are also intended to minimize the potential for unwanted immunogenicity. Animal toxicity studies of the vector, called M87oRRE, have been successfully conducted and plans for first human testing are now being made.

As with any HIV therapy, the emergence of resistance is a concern, especially since resistance to the C36 peptide of T-20 is known to occur clinically. But the scientists found that by extending the length of the peptide with 10 additional amino acids, the resulting C46 peptide was active against C36-resistant isolates, and may be inherently less prone to developing resistance, since the elongation covers a highly conserved region of the gp41 fusion protein missed by C36.

Although still in very early stages, and yet to be tested in humans, this simple and elegant approach to gene therapy to prevent HIV entry into uninfected cells holds exciting prospects.

This report was an update of a poster presented at the 10<sup>th</sup> Annual Retrovirus Conference (CROI) in 2003. Hopefully new progress will be reported at the upcoming conference in San Francisco.

*GMHC Treatment Issues: December 2003, Vol 17, No 12*

## Guidelines for Food and Water Safety for Persons with HIV

Immunocompromised persons are more susceptible to serious food-borne and water-borne illnesses than are persons with stronger immune systems. These secondary infections contribute significantly to the morbidity and mortality of HIV-infected persons. Food plays an active role in disease transmission by supporting the growth of the etiologic agent or toxin production, or a passive role where the food does not support growth but serves as a means of transmission.

Food- and water-borne diseases cause nausea, vomiting, and/or diarrhea with or without additional symptoms of fever, chills, headache and fatigue. Chronic diseases that may result from food-borne diseases include arthropathies, chronic gastroenteritis, organ compromise, and nutritional and other malabsorptive disorders, possibly resulting in death. Cryptosporidium, Microsporidium, Salmonella and cytomegalovirus are the main pathogens resulting in AIDS-related diarrhea. Diarrhea in immunocompromised patients is a challenge for the treatment and prevention of wasting. Fifty percent to 90 percent of persons with AIDS have serious episodes of diarrhea that can be life-threatening.

To prevent or minimize food- and water-borne diseases, the following precautions are recommended in the fifth edition of "Nutrition and Your Health: Dietary Guidelines for Americans," published by the Department of Health and Human Services and the Department of Agriculture. (All temperatures are presented in Fahrenheit degrees.)

- Do not eat raw or undercooked meat, poultry, fish or shellfish. Whole poultry should be cooked to 180 degrees; poultry breast and well-done meats to 170 degrees; and medium-rare beefsteaks, roasts, veal and lamb to 140 degrees.
- Reheat sauces, soups, marinades and gravies to a boil. Reheat leftovers to at least 165 degrees. Use a food thermometer. In a microwave, cover the container and turn or stir the food to make sure it is evenly heated throughout.
- Do not eat raw or partially cooked eggs; foods containing raw eggs; raw (unpasteurized) milk; or cheese made with raw milk. Cook eggs until white and yolks are firm.
- Undercooked hamburger and raw fish (including sushi), clams and oysters are high-risk for contamination. Cook fish and shellfish until it is opaque; fish should flake easily with a fork. When dining out, order foods that have been thoroughly cooked and be sure they are served piping hot.
- When cooking, keep hot foods at 140 degrees or above, and cold foods at 40 degrees or below. In the danger zone between these temperatures, harmful bacteria can grow rapidly. Whether cooked or raw, never leave meat, poultry, eggs, fish or shellfish out at room temperature for more than two hours (or more than one hour if the temperature is 90 degrees or greater). Chill leftovers as soon as possible, and use within three to four days.
- Freeze fresh meat, poultry, fish and shellfish that cannot be used in a few days. Thaw these frozen items in the refrigerator, microwave, or cold water changed every 30 minutes. Cook foods immediately after thawing.
- Uncooked meats should not come in contact with other foods. Hands and all utensils and surfaces should be washed thoroughly after contact with uncooked foods.
- Listeriosis is a serious disease that occurs frequently among severely immunocompromised HIV-infected persons. Some soft cheeses and some ready-to-eat foods (such as hot dogs and cold cuts from deli counters) have been known to cause listeriosis. Reheating these foods until they are steaming can prevent listeriosis.
- Because of the risk of cryptosporidiosis and giardiasis, HIV-infected persons should not drink water directly from lakes or rivers; should avoid swimming in water that may be contaminated with human or animal waste; and should avoid swallowing water while swimming.
- Boiling water for one minute will eliminate the risk of acquiring cryptosporidiosis infection. Using submicron, personal-use water filters or drinking bottled water may also reduce the risk. Current data are inadequate to support a recommendation that all HIV-infected persons boil or otherwise avoid drinking tap water in nonoutbreak settings. Those who choose a personal-use filter or bottled water should

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be aware of the complexities involved in selecting the appropriate products, and the lack of enforceable standards for destruction or removal of oocysts (i.e., tiny eggs), the cost of the products, and the difficulty of using the products consistently.

- Nationally distributed brands of bottled or canned carbonated soft drinks are safe to drink. Also safe are commercially packaged non-carbonated soft drinks or fruit juices that do not require refrigeration until after opening. Nationally distributed brands of frozen fruit juice concentrate are safe if they are reconstituted with water from a safe source. Only juice labeled as pasteurized should be considered free of *Cryptosporidium* risk. Other pasteurized beverages and beers are considered safe to drink. No data are available concerning

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### **HIV BITES** (continued)

become resistant to antiretrovirals. Garlic can have similar effects on AIDS drugs, warned Dr. Charles Farthing, medical director of the AIDS Healthcare Foundation in Los Angeles.

“The simplest thing is to understand one drug and one herb, but the reality is most people are taking more than that,” said Dr. An-Fu Hsiao, lead author of the study. Hsiao’s study was sparked by his long-time interest in alternative medicine and his experiences with HIV patients, some of whom were reluctant to discuss their use of alternative therapies because other doctors had “looked down upon them.”

Hsiao, a University of California-Los Angeles internist, and colleagues at UCLA and RAND Corp. analyzed data from a national survey of 2,466 HIV-positive adults, all of whom had received care for HIV-related illnesses in 1996. The researchers found that 53 percent of study participants used some form of alternative medicine; nearly 26 percent used forms that might be harmful; and 3 percent substituted alternative treatments for prescribed antiretroviral therapy.

While AIDS care providers strongly support alternative therapies like acupuncture, relaxation, massage and hypnotherapy, along with sensible use of multivitamins, they recommend patients avoid herbal remedies or megadoses of vitamins, which can damage the kidneys and other organs. The full study, “Complementary and Alternative Medicine Use of Substitution for Conventional Therapy by HIV-Infected Patients,” is published in the June 1 issue of *Journal of Acquired Immune Deficiency Syndromes* (2003;33(2):157-165). (Los Angeles

survival of *Cryptosporidium* oocysts in wine.

Knowledge of safe food- and water-handling techniques is essential for persons living with HIV and AIDS, their caretakers, and for health care providers to prevent the potentially life-threatening nature of such infections. To decrease the risk of infection from enteric pathogens, emphasis should be placed on proper storage or perishable foods, adequate cooking of animal foods, avoiding cross-contamination of raw and cooked foods, ensuring appropriate sanitation in the kitchen, ensuring personal hygiene, and using water from safe sources.

*From the National Prevention Information Network (NPIN) of the Centers for Disease Control and Prevention (CDC) Body Positive Vol. XVI, No. 5, 2003*

Times (06.23.03)::Jane E. Allen) *Body Positive Vol. XVI, No. 5, 2003*

### **Herbal Supplements Can Reduce Effectiveness of Prescription Drugs**

(From *UC Berkely Wellness Letter*, May '00, April '02, and February '03)

Think twice about taking herbal supplements.

#### **Garlic**

An NIH study published in *Clinical Infectious Diseases* showed that the blood levels of the protein inhibitor saquinavir dropped 51% when taken with garlic supplements. Other HIV drugs, and possibly drugs for other diseases, may also be affected. Garlic supplements are also known to interfere with blood clotting.

#### **St. John’s Wort and Echinacea**

Similarly, several studies have found that St. John’s Wort, which some believe relieves depression, interferes with some HIV drugs and other drugs. Another herb, Echinacea, which is used in the hope of boosting the immune system and reducing cold symptoms, should not be used by those with compromised immune systems or auto-immune diseases or undergoing chemotherapy.

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# One for the Blipper

By Bob Huff

You can be a “blipper” and still be chipper, suggests a study in the Nov. 2003 issue of the *Journal of Virology* by Michele Di Mascio and her colleagues from the Los Alamos National Research Center in N.Y. Blips are usually thought of as occasional, transient, episodes of low-level HIV RNA viremia in someone who is adherent to their antiretroviral therapy and otherwise enjoys a well-suppressed viral load. Most people with HIV RNA below 50 copies/mL (undetectable) may have intermittent positive viral load test results at some time or another. But how common are blips, how long do they last, and what causes them?

Some have suggested blips are due to the release of virions from reservoirs or protected sanctuaries in the body where replication of drug-sensitive virus continues at a low level. Others have reported that it's drug-resistant virus that makes for blips. Another theory is that an immunological event such as an infection suddenly increases the number of infectable immune cells and blips are the resultant viral feeding frenzy. Whether due to natural variations in drug levels in a person hovering on the margins of suppression, most studies have not found a long-term association between blips and loss of virologic control or disease progression.

Di Mascio's study looked carefully at the frequency and duration of blips above 50 copies/mL as recorded in 123 treatment naïve patients from 8 different research cohorts starting a PI-containing regimen. The mean CD4 count at treatment initiation was 474 (+/- 254) cells/mm<sup>3</sup>. Overall, the analysis looked at an average of 26 viral load tests per subject over as many months, with 41 patients showing no blips and one patient blipping at every other determination. The average number of blips per sample was 0.09.

The study found that blips were not due simply to assay variation or to chance alone but that different people inherently have different tendencies to blip. They next showed that, within limits of monthly testing, having one blip does not predict having another and that blip arrival is substantially random. Also, in the patients studied, neither the frequency nor amplitude of blips seemed to increase with time on therapy, which suggests that poor adherence was not responsible for these viremic episodes. There was a relationship between blip frequency and baseline CD4 count, with those having more advanced HIV disease at the time of starting therapy being more likely to become blippers. The significance of this is not clear, although, during the period of observation reported here no increase in blip frequency was seen.

## Blips Passing in the Night

Perhaps the study's most striking finding is that blips may actually be viremic episodes that last as long as a month, and that, depending on sampling frequency, a number of different blips could produce a pattern of viral load test results that appears as continuous viral breakthrough. An analysis of viral load measurements taken within 22 days of a blip, when fitted into a model, predicts a typical blip duration of 20 to 30 days. If blip episodes actually last this long, then even people with several consecutive detectable viral load determinations might actually be having a train of independent blips, and not sustained viral load throughout the period. Since even sequential blippers in this study generally did not progress to virologic failure, one might wonder how many consecutive blippers in real life have undergone unnecessary regimen switches because of what appeared to be sustained low-level viremia to a clinician determined to maintain undetectability? While this work comes from the Theoretical Division of the Los Alamos lab, the practical implications of blips, blippers and blipping obviously require more and urgent research.

## Replication Rates and Viral Load

The different rates and amplitudes of blipping suggest that there is a great deal of individual variability in the replication rate of HIV, even when mostly suppressed by drug pressure. Another study reported in the Nov. *Journal of Virology* investigated the relation between viral load and replication rate in individuals who are not taking antiretroviral drugs.

It's long been recognized that viral genetics plays a role in how aggressively HIV behaves in a host. The X4 coreceptor-using variant is particularly famous for kicking HIV immune damage into high gear. More recently it's been recognized that for people who have been on therapy and have developed drug-resistance, their mutant virus may be “less fit” than a wild type drug-susceptible virus. So, staying on a failing regimen may be clinically protective despite loss of viral control. Growth competition experiments have also shown that viruses from several long-term non-progressors were inherently less replication competent than viruses from people with normal rates of disease progression.

On the host side, the best known genetic trait that affects susceptibility to HIV infection and subsequent disease progression is a mutation found in a small segment of the population that limits or eliminates the CCR5 cell surface protein, an essential co-receptor for HIV entry. But this flaw in the CCR5 gene is not the only source of CCR5-dependent variability in HIV repli-

cation. Even in person with 2 functional copies of the CCR5 gene there may be considerable interpatient variability in levels of CCR5 expression at the cell surface. Individuals may also express different amounts of RANTES, a messenger protein that competes with HIV for using CCR5, with elevated levels of RANTES associated with slower disease progression. Different degrees of innate and acquired immunity to HIV may also play a large role in keeping HIV replication under control during the years of slowly progressing disease that follows primary infection. HIV-specific CD8 cells in particular are thought to help in controlling runaway HIV disease and it is hoped that one day a vaccine can be made to boost these protective cells.

The amount of virus found in the blood (viral load) is likely determined by a balance between the elimination of virus and the production of new virus. HIV-specific CD8 cells are generally considered the leading candidate for effecting viral elimination. But this theory remains shaky because most studies haven't found the expected correlation between the strength and specificity of CD8 T-cell response and lowered viral load. If CD8 are mainly responsible for clearing out unwanted HIV, then why don't people with the most qualified CD8s always have the lowest viral loads?

Thomas Campbell and colleagues from the University of Colorado, Denver, sought to establish if replication rate was correlated with plasma viral load levels by performing two different kinds of replication rate assays on the viruses of 12 individuals with chronic HIV infection who were not receiving treatment. Eight of the 12 were treatment naïve and none of the participants had detectable drug resistance mutations.

Each individual's virus was cultivated in cell cultures for up to ten days with assessments of HIV p24 protein production performed daily. Changes in the amount of p24 detected from one assessment to the next produced a growth curve that revealed each virus' particular replication dynamics. Typically, each virus had a daylong lag before any p24 production was seen. After p24 was detected, growth proceeded exponentially for the next 6 days or so. A plateau phase appeared after the 6th day when additional p24 production tapered off, probably due to saturation of infectable cells after day four.

In addition to the growth curves, the replication capacity of each virus' reverse transcriptase and protease enzymes were determined by genetic recombination techniques using a modified version of the Phenosense drug susceptibility assay.

The investigators found a strong linear relationship between replication rate and viral load that held true from 1000 copies to 100,000 copies/mL. Furthermore, they

established that, among these 12 individuals, there was significant natural variation in rates of viral replication due entirely to viral qualities. Another interesting finding was that RT and PR replication capacity were related to the cell-based replication rate. This suggests that genetic variations in these wild type enzymes may be responsible for the different replication rates of different viruses, even in the absence of drug exposure.

One limitation to the study is that in cell systems the role of the host's genetics and immune system are removed, so an individual's actual response to their virus can not be predicted from these results. This issue aside, the authors make a provocative suggestion that different viral replication rates may be obscuring measurements of immune-based factors that influence HIV viral load in the body. In particular, they suggest that CD8 cell responses, which have previously not correlated well with viral load, should be reexamined after controlling for replication rate. It's possible that the expected CD8 impact on viral load may only become clear after the "noise" of variation in replication rate has been reduced. If so, then this could help unlock one of the central mysteries of immune control of HIV and remove one of the stubborn stumbling blocks in the way of finding a vaccine. *GMHC Treatment Issues; Nov. 2003, Vol 17, No 11*

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**Toro Study Design:** Toro 1 [T-20(Fuzeon) vs. Optimized Regimen Only] and Toro 2 are randomized, open-label trials that enrolled approx. 1,000 HIV-1 infected patients at 112 centers internationally. Patients were treatment-experienced and/or had documented resistance to each of the other 3 classes of anti-HIV drugs. At entry, resistance testing and patient treatment history were used together to aid in the selection of an individualized regimen of 3-5 anti-HIV drugs for each patient. After selection of the regimen, patients were randomized 2:1 to receive either the regimen in combination with Fuzeon (Fuzeon arm) or the individualized regimen alone (control arm). At baseline, patients had a median HIV RNA level of more than 5/0 log<sub>10</sub> copies/mL, a median CD4 cell count of less than 100 cells/mm<sup>3</sup>, and were treated with anti-HIV drugs for average of 7 years.

**Fuzeon Indication & Safety;** Fuzeon in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of Fuzeon of 24 weeks' duration. Subjects enrolled were treatment-experienced adults; many had advanced disease. There are no studies of Fuzeon in antiretroviral naïve patients. There are no results from controlled trials evaluating the effect of Fuzeon on clinical progression of HIV-1. *PR Newswire, Sept. 15, 2003*

## Choose HIV Drugs that Work for You

By Frank Pizzoli

Ever hit a restaurant with a menu bigger than your apartment? You need food, but the choices are staggering. HIV drugs are similar. Current information empowers consumers to make “informed” choices when choosing HIV drugs.

**KNOW YOUR GOAL:** HIV treatment’s ultimate goal is to preserve infection-fighting CD4 cells by lowering your viral load (VL) to an “undetectable” level for as long as possible. Ideally, you want your VL to remain undetectable, which means there are fewer than 50 virions (particles of the virus) per millimeter of blood—the lowest amount blood tests can measure. Below 50, fewer CD4 cells are being attacked by the virus than if VL is higher. Protecting CD4 cells from viral attack is paramount because they fight off nasty, sometimes life-threatening, infections.

**KNOW YOUR CHOICES:** When choosing HIV drug combinations remember it’s one thing to initially achieve lower VL. It’s another to sustain that lowering over time. Although most combinations initially lower VL, some drugs are simply better at keeping VL lower for longer periods of time.

Here’s shorthand for the five different HIV drug classes from which “combinations” are selected: two types of “nukes” (nucleoside and nucleotide reverse transcriptase inhibitors), “non-nukes” (non-nucleoside reverse transcriptase inhibitors), protease inhibitors, and fusion inhibitors. Combinations should include at least three different drugs. For initial therapy, the Federal Government recommends certain “preferred” drugs for a combination of either two nukes plus a protease inhibitor or two nukes plus a non-nuke.

In chart form, you’d see 23 choices of medicine made from 19 different compounds. (The additional choices are actually combinations of two or three of the 19 compounds.) Although there are 23 meds, the number of effective combinations that you can choose is limited. Therefore, you’ll want to choose drugs that will not only reach your goal of undetectable as fast as possible, but that will keep HIV as low as possible for as long as possible. That’s also exactly what the new Federal Guidelines stress: “Treatment goals should be maximal and durable suppression of viral load.”

**DRUG INTERACTIONS:** In addition to how well and for how long a combination keeps viral load undetectable, you’ll want to consider possible side effects

and drug interactions. Because of the way some drugs interact with others, certain HIV drugs should never be taken together. In fact, you should make sure your doctor knows everything you’re taking, including vitamins and recreational drugs. Interactions are a big deal.

As far as side effects, all HIV drugs can cause them. But the fewer and milder the side effects, the better. Keep in mind that this is a very individual thing. Side effects vary from drug to drug, and even among different individuals taking the same drug. So consider your lifestyle. For example, if you have a job where you have to be mentally alert, drugs that make it hard to concentrate may not be right for you.

**REQUIREMENTS:** To lower the number of pills taken daily, called “pill burden,” there are HIV meds that combine two or three drugs into one pill. This can make adherence more convenient. So can combinations that are taken fewer times during the day. Although dosing convenience is a nice quality in a drug combination—especially once-a-day convenience—it isn’t the best or only reason to choose one drug over another. “Convenience” doesn’t automatically make a regimen effective at keeping VL low for as long as possible. The true measure of success is how long your VL stays undetectable. In fact, recent Federal Government Guidelines noted a major concern about once-daily therapy over “the paucity (lack of) of long-term trials with comparison to potent twice daily regimens.”

There are also the issues of food requirements. Some HIV drugs have food requirements which means they are taken with or without food, or with particular types of food. Some drugs have easier food rules than others. For example, some nukes have no food restrictions, but others must be taken with meals. Non-nuke drugs have no restrictions. And depending on the drug, protease inhibitors are taken with or without food. Some HIV drugs have no food restrictions and are taken at meal time, almost like a built in reminder when to take them. But having to take one drug with food and another without food can be a hassle. With or without food requirements, the main goal is to pick drugs that will keep your VL as low as possible for as long as possible.

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# Trying to Eliminate HIV by Luring Virus Out of Hiding

(From The New York Times, 9/23/03)

The AIDS virus has the power to hibernate, virtually forever, even in patients taking their meds. Many AIDS specialists are working on ways to tease the virus out of hiding so it can be killed, and real progress has been made. A U.C.L.A. laboratory recently reported 80% success in mice. Even that, however, cannot stop the virus from roaring back. "Eighty percent is close," said Dr. Roger J. Pomerantz, an AIDS researcher in Philadelphia. "But close only counts in horseshoes and hand grenades."

Even if the virus, battered by antiretroviral therapy, is founding just one dormant T cell in a million, repeated tests in humans have shown that it will re-emerge if the therapy stops. Simply hunting it is a ticklish business, because the virus hides in the same memory T cells that act as triggers for the immune system. Failing to "light up" the virus in them will keep it hidden. But activating too many T cells means a cascade of immune reactions like those in toxic shock syndrome, possibly killing the patient.

Since beginning their quest 19 years ago with the realization that infected T cells somehow slept in "reservoirs" in the lymph glands, blood and perhaps in parts yet unknown, researchers have experimented with immuno-boosting drugs borrowed from cancer therapy and with tiny "smart bombs" that use antibodies and kill HIV with a minuscule dose of poison. Despite regular advances, some prominent AIDS researchers worry that the task may be hopeless.

"It's very, very, very difficult situation," Dr. Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases, said. "You can get a reservoir down to an undetectable level, and then if someone gets even a little blip of viremia, it can reseed the area, and you're back to Square One." That "blip of viremia," a jump in virus circulation in the bloodstream, can be set off even by a bout of flu or a rusty nail, because the AIDS virus can hide in a T cell that normally attacks the flu virus or tetanus.

Dr. Robert C. Gallo, director of the Institute of Human Virology at the University of Maryland, said many labs had attacked latent virus, with no breakthrough success yet. The newest work, at U.C.L.A.'s AIDS Institute, was in mice bred without immune systems in which human thymus cells were implanted and infected. Although he praised the research, Dr. Gallo said the mouse-thymus models was "a very artificial system. ... If you had this

in a monkey model, with demonstrable safety data," he said, "that would merit highlighting it." If humans were given big enough doses to reach the most hidden cells, "I don't know that it wouldn't be terribly dangerous," Dr. Gallo said.

HIV is frequently described as wily for its ability to mutate into drug-resistant forms. But it is equally wily in its hibernation style, sitting as silent as a nuclear submarine on the ocean floor. Incorporated into the DNA of a shrunken, inactive T cell, the virus is a mere speck of genetic code, 10,000 base pairs out of the 6 billion in each human nucleus. "It exists as pure information," said Dr. Robert F. Siliciano, a Johns Hopkins' AIDS researcher. "The immune system can't see it, because the system sees proteins, and it's not making proteins. The drugs don't touch it, because they stop replication, and it's not replicating." Dr. Siliciano recently demonstrated that the numbers of infected dormant cells remained steady over 7 years and might take 70 years to die off under normal antiretroviral assault.

Trying to defeat that, researchers try ever more complicated regimens. Dr. Fauci described treating 10 patients with multiple cycles of interleukin-2 to "flush the virus out. ... We thought the cells would spit out their virus and die, which would take care of those suckers, and then antiretrovirals would stop proliferation," he said. After a moment of jubilation when he found no virus even in biopsies from his patients' lymph nodes, he went for "the proof of the pudding" and took the patients off their AIDS drugs. "Everyone rebounded," he said. "We failed."

In the U.C.L.A. study, prostratin and interleukin-7 were chosen to "tickle the cell, just turn the virus on without turning on the cell." A "turned-on" virus displays some of its proteins on the surface of the T cell, but does not prod the cell to divide or to wake up other T cells to begin an immune system assault on a foreign invader. "Then we come in with the immunotoxin," said a team leader, Dr. Jerome A. Zack. It is a molecule-size smidgen of bacterial poison attached to an antibody that gloms onto the T cell and injects the toxin. "Immunotoxins are too poisonous to use alone against AIDS, but they may work in combination with antiretrovirals," he said. If all goes well, he will try the tactic in monkeys and then humans.

*HIV Notebook, Winter 03-04*

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## Herbal Supplements (continued)

### Grapefruit Juice Also a Problem

(From *Harvard Health Letter*, Jan. 2003)

Grapefruit juice boosts the effect of many medications and reduces the strength of others. The list of drugs affected has grown. Unless your doctor tells you to wash your pill down with grapefruit juice to increase its effect, you don't want to do it. It might seem like a good idea to improve the level in your body of the drug so simply, but the dosage is determined by studies and your doctor's knowledge of you. Drinking juice would be like deciding if two pills are good, three would be better. In fact it could be worse, because you would not have control of the amount of drug in your system.

Some of the literature suggests avoiding grapefruit juice and grapefruit entirely. Some of the effects linger in the body for days. Others point out that the absorption enhancing effect of grapefruit juice tapers

off over time, so if you take your meds in the morning and drink a glass of juice at night the effect is far less than if you take them together.

**Oranges:** Most oranges and orange juice consumed in the United States do not contain the substance believed to create the problem which arises from drinking grapefruit juice. But Seville oranges (used to make some marmalades) and tangelos (a grapefruit hybrid) do, so they may also affect absorption of some drugs.

## HIV Notebook, Winter 2003-2004

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## Choose HIV Drugs that Work (continued)

**ADHERENCE AND RESISTANCE:** All medicines work to some degree, but only if you take them. Remember being warned to finish all your antibiotics because stopping them prematurely allows the rash to return? Same result with HIV drugs, only it's called "resistance".

Resistance to your HIV meds means your drugs can no longer fight off the virus. This can happen if the HIV virus evolves in such a way that it enables new copies of itself to survive in the presence of the drugs you're taking. Missing doses can result in the amount of medicine in your blood dropping below levels needed to control the virus. Uncontrolled, the virus will then be free to invade infection-fighting CD4 cells. As more and more CD4 cells are destroyed, you are much more likely to develop opportunistic infections. This "chain reaction" concerns the Federal Government, which notes that "missing one [once-daily] dose may result in inadequate drug exposure over a defined period of time leading to a higher probability of development of drug resistance."

To avoid resistance, research indicates HIV drugs must be taken 95 percent of the time. Even if taken

95 percent of the time, some people still develop resistance. And even with less than perfect adherence, resistance doesn't always develop. The point is that some HIV drugs are "more forgiving" and others "less forgiving" if you miss doses. Try to pick drugs with a good track record at keeping HIV undetectable and avoiding resistance.

**EFFECTIVENESS:** Whether you're starting HIV therapy for the first time or switching regimens, it's important to choose drug combinations that keep your VL undetectable for as long as possible. And that's regardless of the number of pills required on a daily basis. Of all the factors you'll consider, remember that there's no relationship between the "convenience" of taking fewer pills and their "effectiveness." The fact of the matter is that some drugs are simply better at keeping VL undetectable for the long haul. And to these drugs, there are options. Don't trade off "today convenience" for "tomorrow's effectiveness."

*Frank Pizzoli writes frequently for Body Positive, and also contributes to Instinct, POZ, and New York Blade News. He founded the non-profit Positive Opportunities (PosOps@aol.com), which offers educational seminars and benefits counseling to HIV-infected people through support from Broadway/Equity Fights AIDS and the Greater Harrisburg Foundation*

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# Protease Inhibitors and Bleeding in HIV Positive Patients

By Bruce L. Evatt, *Haemophilia* 2002)

Highly active anti-retroviral treatment (HAART) has dramatically influenced the clinical course of HIV infection by increasing survival and reducing complications. HIV protease inhibitor (PI) drugs have been a major component of HAART regimens.

Soon after the introduction of the first PI drugs (ritonavir, indinavir and hard gel saquinavir in the mid-1990's), there were a number of reports of increased bleeding among patients who were being treated with these drugs. Interestingly, however, the more recently introduced PI drugs, including nelfinavir, amprenavir and lopinavir (or the lopinavir/ritonavir combination) do not appear to be associated with an increased bleeding tendency. This lack of bleeding association would be consistent with the overall markedly reduced toxicity of these drugs compared with ritonavir and indinavir.

The increased bleeding tendency among patients taking PI drugs has been characterized in two large case studies. In one of them, 34 (51%) of the 67 patients taking the drugs bled more frequently. Bleeding usually occurs within the first few weeks after a patient begins therapy, although some patients have increased bleeding almost immediately, while others may not have increased bleeding for several months.

Ritonavir has been associated with the highest incidence of bleeding, followed by indinavir. Saquinavir, as a single therapy, does not appear to present a risk of bleeding. However, PI combination regimens including saquinavir (e.g., ritonavir/saquinavir) have been associated with an increased bleeding tendency.

The most common hemorrhagic manifestation is an increased frequency of muscle and usual "target" joint bleeds. However, patients have also reported subcutaneous, soft tissue and mucous membrane bleeding that they had not previously experienced. Bleeding in unusual places, such as the small joints of the hands and the soft tissue of the palms and the soles, has also been observed. Macroscopic hematuria (blood in the urine) has been reported in association with both ritonavir and indinavir. Indinavir-induced hematuria appears to be a direct bleeding effect and distinct from the indinavir-induced loin pain syndrome. Intracranial bleeding and bleeding into the cervical and thoracic spine and retina have also

been reported.

Frequently, patients with bleeding respond poorly or not at all to regular doses of factor concentrate replacement therapy. Commonly, larger doses of concentrate than usual are required to stop bleeding, and repeated doses need to be administered. Prophylactic factor concentrate has been effective in treating some individuals with particularly troublesome bleeding. However, some patients with severe bleeding have had to discontinue their use of PIs in order to alleviate the bleeding problem. Interestingly, the substitution of one PI for another usually causes the increased bleeding to cease, although in many patients who persevere with their first-line PI therapy, the bleeding tendency may resolve with time.

Some patients who have not experienced an increase in spontaneous bleeding while taking PIs have developed excessive bleeding in association with surgery and dental extractions. It is therefore very important to be aware of this, regardless of whether there has been a previous problem with bleeding associated with these drugs. Consideration can be given as to whether to temporarily discontinue the use of the drugs for these procedures, with the caution that resistance to PIs may develop during lapses of therapy.

The mechanism of increased bleeding associated with PI therapy remains unexplained. The reduced efficacy or even failure of factor replacement therapy among hemophilic patients and the occurrence of bleeding that has been reported among non-hemophilic individuals suggests that PIs do not directly exacerbate the inherently increased bleeding risk of people with low FVIII and FIX levels. Furthermore, studies of patients with PI-associated bleeding have shown that their levels of coagulation factors, von Willebrand factor, and functional fibrinogen are not significantly affected by PI therapy.

The lack of consistent evidence that PIs increase the users' tendency to bleed by disturbing either the function of clotting factors or platelets suggests that they act independently of the circulatory component elements of hemostatic balance. Instead, they may have a local effect on the integrity of blood vessels, perhaps by disturbing vascular cell functions.

## **New Data Show Fuzeon-Based Regimens Continue to Provide Significant Durable Response in Treatment-Experienced HIV Patients Through 48 Weeks**

### **Reimbursement Progress and Increased Supply Diminish Early Concerns About Limited Access to Fuzeon**

Eighty percent of patients receiving a Fuzeon® (enfuvirtide)-based anti-HIV drug regimen who achieved undetectable levels of the virus at 24 weeks maintained this response at 48 weeks, according to new data presented today at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). Researchers also reported that 37% of heavily treatment-experienced patients treated with a Fuzeon-based combination maintained at least a 90% (or 1.0 log<sub>10</sub>) reduction in blood levels of HIV at 48 weeks, vs. 17% of patients on a regimen without Fuzeon. Previous clinical studies in HIV have shown that a 68% (or 0.5 log<sub>10</sub>) reduction in HIV levels may be associated with clinical benefit to patients. Co-developed by Roche and Trimeris (Nasdaq: TRMS), Fuzeon was granted accelerated approval by the US Food and Drug Administration (FDA) in March and is the first and only approved fusion inhibitor for the treatment of HIV.

“These results are encouraging because they demonstrate the utility of Fuzeon-based regimens at nearly one year, regardless of the treatment goal for each individual patient,” said Daniel R. Kuritzkes, MD, Director of AIDS Research at Brigham and Women’s Hospital and Associate Professor of Medicine at Harvard Medical School. “Adding Fuzeon to a regimen of tailored anti-HIV drugs doubles the likelihood that treatment-experienced patients will achieve undetectable HIV levels at 48 weeks. For patients with more advanced disease, Fuzeon-based combinations may still provide meaningful reductions in HIV levels and improvements in immune system status over the long-term.”

### **Fuzeon 48-Week Safety and Efficacy Data**

Additional 48-week results from the Phase III trials of Fuzeon found that among patients who achieved undetectable levels HIV at 24 weeks, a higher percentage of patients in the Fuzeon arm maintained this response at 48 weeks compared to patients on a regimen without Fuzeon (80% vs. 70%). At 48 weeks, more than twice the percentage of patients in the Fuzeon arm had undetectable levels of HIV (less than 400 copies/mL) compared to patients on a regimen without Fuzeon (30% vs. 12%).

Study results show that, on average, patients receiving a Fuzeon-based regimen experienced an increase of

twice as many immune (CD4) cells as those achieved by patients on a regimen without Fuzeon (increase of 91 cells/mm<sup>3</sup> in the Fuzeon arm vs. 45 cells/mm<sup>3</sup> in the control arm at 48 weeks, and increase of 71 cells/mm<sup>3</sup> in the Fuzeon arm vs. compared to 35 cells/mm<sup>3</sup> in the control arm at 24 weeks). In addition, the time to virologic failure was approximately three times longer on the Fuzeon arm compared to patients on regimens without Fuzeon (32 weeks vs. 11 weeks). All of these results were highly statistically significant (p<0.0001).

The superiority of virologic response achieved with Fuzeon-based regimens was observed regardless of the number of active agents in the background regimen. Among patients whose virus was sensitive to one drug in the background regimen, more patients in the Fuzeon arm achieved undetectable levels of HIV compared to patients on regimens without Fuzeon (29% vs. 7%). Among patients whose virus was sensitive to two active agents in their background regimen, more patients achieved undetectable levels of HIV in the Fuzeon arm at 48 weeks compared to patients on regimens without Fuzeon (39% vs. 15%). These results were statistically significant (p<0.05).

A detailed 48 week safety analysis was also presented. Ninety-eight percent of patients experienced a localized reaction at the site of injection, such as pain/discomfort, redness, hardness, bumps, itching or bruising. Less than 5% of patients discontinued treatment due to injection site reactions. Aside from injection site reactions, the incidence of the 3 most common adverse events, measured as number of events per incidence of the 3 most common adverse events, measured as number of events per 100 years of patient experience was less frequent in the Fuzeon arm compared to control arm. Adverse events included diarrhea (37 per 100 patient-years in the Fuzeon arm vs. 73 in the control arm), nausea (26 vs. 51, respectively) and fatigue (25 vs. 38, respectively). (See “Facts about Fuzeon” section for more info)

“Safety is a crucial consideration for physicians and patients who are selecting a new anti-HIV drug regimen,” said Joseph Eron, MD, Associate Professor of Medicine, University of North Carolina at Chapel Hill. “In these studies, Fuzeon did not ex-

acerbate most of the adverse events commonly associated with other anti-HIV therapies. In fact, patients who received Fuzeon as part of an anti-HIV drug regimen experienced less diarrhea, nausea and fatigue. These results are very encouraging for physicians and patients who are considering initiating use of Fuzeon.”

**Reimbursement and Supply Progress Increase Access to Fuzeon in the US**

During the first 6 months post-approval, Roche and Trimeris have worked closely with both public programs and private insurers to secure reimbursement for patients who need Fuzeon. Fuzeon is now on the formularies of all state Medicaid programs, the Veterans’ Administration, and 28 AIDS Drug Assistance Programs (ADAPs), which represent 75% of patients who receive their HIV drugs from an ADAP. ADAP programs currently covering Fuzeon include:

Alaska	Maine	Pennsylvania
Arizona	Massachusetts	Puerto Rico
Arkansas	Michigan	Rhode Island
California	Minnesota	S. Carolina
Connecticut	Mississippi	Tennessee
Delaware	Missouri	Utah
Florida	New Jersey	Virginia
Illinois	New York	Wisconsin
Iowa	N. Carolina	
Kansas	Oregon	

“In spite of severe fiscal challenges facing California’s ADAP, we felt it was critical to provide access to Fuzeon to our ADAP clients, especially to those who have become resistant to existing HIV medications. We appreciate the willingness of Roche to work with the ADAP Crisis Task Force to make Fuzeon more widely available,” said Michael H. Montgomery, Chief, Office of AIDS, California Dept. of Health Services.

“The majority of private and public insurers in the US have now added Fuzeon to their formularies, significantly reducing the time required to process prescriptions,” said Gary Zieziula, VP, Commercial Operations, Roche. “Broader reimbursement, combined with greater than anticipated supply, means expanded access to Fuzeon.” Roche and Trimeris also offer a Reimbursement Assistance Program to support patients and physicians in the reimbursement process, and a Patient Assistance Program which provides Fuzeon free of charge to patients who are uninsured, are US residents and meet specific requirements.

Roche and Trimeris have continued to invest in improving Fuzeon manufacturing, contributing to increased drug supply. A manufacturing process modification which has been filed in the US and EU is now leading to improved outputs of Fuzeon active pharmaceutical ingredient (API). Also, installation of a second chromatog-

raphy column was achieved ahead of schedule. The column is currently undergoing validation and will have the potential to increase the capacity at Roche’s facility in CO. Finally, plans are now in place for significant further expansion of the Boulder facility that will increase the current planned capacity of 3.7 metric tons per year to around 6 metric tons per year in 2005. T-1249 Update.

A final analysis of data from the Phase I/II study of the second-generation fusion inhibitor, T-1249 was presented yesterday in an oral presentation by Dr. Jacob Lalezari of Quest Clinical Research in San Francisco. This 10 day study included 53 patients who were participating in Phase II or Phase III studies of Fuzeon and who exhibited HIV RNA levels between 5000 and 500,000 copies/mL at 2 consecutive clinic visits while on treatment with Fuzeon. Patients in the study discontinued Fuzeon and added T-1249 to an unchanged individualized anti-HIV drug regimen. At day 11, 73% of patients demonstrated a greater than 1.0 log10 reduction in HIV RNA. Safety evaluations revealed no serious adverse events relating to T-1249. The most frequent adverse events were joint pain (4%), diarrhea (4%), fatigue (4%), muscle pain (4%) and fever (4%).

“ Roche and Trimeris are applying our experience from the development of Fuzeon to our continuing search for new treatment options,” said Dr. Dani Bolognesi, CEO, Trimeris. “The results from this study of T-1249 demonstrate that fusion inhibitors constitute an expanding class of anti-HIV drugs with the potential to be used sequentially.”

The next step in the development of T-1249 will be Phase II studies, which are projected to begin in 2004. The initiation of these trials is dependent upon a combination of factors including scale-up of manufacturing, completion of formulation work to support chronic dosing, finalization of clinical protocols, and regulatory discussions. For more info on Fuzeon, visit [www.FUZEON.com](http://www.FUZEON.com) or call 1-877-4FUZEON.

**Facts About Fuzeon**

Fuzeon, co-developed by Roche and Trimeris (Nasdaq: TRMS), was granted accelerated approval on the basis of 24-week data by the US FDA in March and is approved in the European Union, Switzerland and Canada. Fuzeon leads the first class of anti-HIV drugs to be introduced in 7 years. Unlike other HIV drugs that work after HIV has entered the human immune cell, Fuzeon works outside the CD4 cell, blocking HIV from entering the cell. For this reason, Fuzeon is effective in treatment-experienced patients who have developed resistance to other anti-HIV drugs, though patients may still develop resistance to Fuzeon.

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*It seems rather  
incongruous  
that in a society of  
supersophisticated  
communication,  
we often suffer from  
a shortage of listeners.*

*Erma Bombeck*

